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Refractory Ulcerative Proctitis—A Brief Review

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Abstract

Ulcerative proctitis (UP) is a common condition in adult patients and can be very difficult to treat. This review considers critically the definition of this entity, its epidemiology and course, and the modes of therapy currently available. Therapies currently in development are considered as well.

Keywords

Ulcerative Proctitis, Epidemiology, Therapy

1. Introduction

Ulcerative proctitis (UP) is part of the spectrum of ulcerative colitis (UC), which is the commonest form of inflammatory bowel disease (IBD) in most geographical localities. The condition affects the rectum and varies in its clinical manifestations from mild to severe or very severe. A variety of treatments is in use, but the refractory cases pose a tremendous clinical problem requiring drastic therapies. In this review, the nature of the condition, its clinical manifestations and treatments are described, and avenues for future therapeutic approaches are indicated.

2. What Is Proctitis?

Ulcerative proctitis (UP) is part of the spectrum of ulcerative colitis (UC), which is the commonest form of inflammatory bowel disease (IBD) in most geographical localities. By the Montreal classification (E, S, A), UC can be divided into three broad phenotypes based on disease extent (E) in the rectum and colon. E1 is ulcerative proctitis, E2 is left-sided or distal colonic disease, and E3 is extensive or total colitis [1]. UC always involves the rectum, and has the potential for variable proximal extension. UP is specifically defined by the disease extent parameter, as disease involvement limited to the rectum, and therefore is located distal to the recto-sigmoid junction. Disease activity (S) of all these phenotypes is defined as S0: asymptomatic (remission), S1: mild (up to 4

stools per day, with or without blood, but no systemic features allowed), S2: moderate (more than 4 stools and minimal systemic toxicity), and S3: at least 6 bloody stools per day, rapid pulse, anemia and fever. Finally, patient age (A) at onset is a defining epidemiological feature: A1 ≤ 16, A2 17 - 40, A3 > 40 years. UP is a therefore a disease of part (or all) of the rectum, with a spectrum of clinical severity, and onset in all age groups but mostly 17 - 40 years. It presents with diarrhea, frequently with mucus and blood in the stool, often with urgency, tenesmus and rectal or anal discomfort, while systemic symptoms are usually absent. The typical endoscopic appearance of inflamed rectal mucosa, the classical continuous distribution of small ulcers, mucosal friability and contact bleeding are all pathognomonic features of UP, as they are of UC. It must be remembered however that Crohn's disease, with its cobblestoned mucosa and irregular, large and deep ulcerations can occasionally occur confined to the rectum [2], and the distinction from UP is important since the treatment and prognosis are very different. Ischemia in the rectum, radiation-induced proctitis, toxic injury, infections like cytomegalic virus and *Clostridium difficile* pseudomembranous colitis, parasites and sexually-transmitted diseases all enter into the differential diagnosis of UP [3]. The etiology of UP is likely the same as the etiology of UC, which is to say that it is basically unknown. Studies of etiology in UC focus on genetic and environmental factors: many aberrant genes were identified, dietary habits including fiber intake, linoleic acid intake, animal protein and breast-feeding were considered, exposure to infections in childhood and use of antibiotics, seasonality and geographic variations in incidence. The only clear associations are that current smoking (though not advised to patients!) and appendectomy (see below) are protective in UC, and possibly also in UP [4].

3. Incidence

The incidence rate of UC and therefore of UP has been variably reported all over the world. In the USA it was given as 7 - 9 cases per 100,000 population per year, with a point prevalence rate of 200 - 250 cases per 100,000 population [5]. Most cases of UC start as UP (E1) or distal colitis (E2). The point prevalence rate of UP at diagnosis is not the same as the rate on follow-up, since UP is known to progress in extent and become distal or extensive UC over time in a proportion of cases. How many prevalent chronic UC cases meet the Montreal E1 criterion of UP is unclear, but several reports have tried to answer this question. In the classical Olmsted County paper the ratio of extensive UC, distal UC and UP was 4.5:2.6:1.1 in the decade ending 1993 [6]. The more recent IBSEN study which was carried out in the years 1990-1994 reported a ratio of 3.2:3.5:3.3, so that the proportion of UP was threefold higher [7]. Likewise from Copenhagen the reported ratio was 2.7:4.2:3.1 at time of diagnosis in the years 2003-2004. This represented a relative increase in the rate of UP in Copenhagen since the study began in 1962 [8]. In the EpiCom 2010 incidence cohort 20% of UC cases in Western Europe and 22% in Eastern Europe were defined as UP at presentation (5-year follow-up data are due to be published in the next year) [9]. The most recent report was a Swiss study, which found a ratio of 4.2:3.7:2.2 for extensive UC, distal UC and UP at time of diagnosis [10]. In summary, 22% - 33% of UC cases present as UP at time of disease diagnosis.

4. Course over Time

Course refers to extension, level of clinical activity and refractoriness. An intriguing question is what proportion of cases do not extend proximally but remain as UP over time. In an analysis from the Swiss IBD cohort study it was found that one-third of patients increased their initial disease extent over a median follow-up period of 9 years [10]. Likewise, an Italian study found that 27% of UP cases had proximal extension over a mean follow-up period of just 5 to 6 years [11]. In the Norwegian study with 10 years of follow-up, 42% of UP patients showed proximal extension to left-sided or total colitis [7]. These data would indicate that the majority of UP cases remain as UP over time. Factors that predicted proximal extension of UP included smoking, chronic active or refractory disease, and a need for corticosteroids or immunomodulators, but not gender, age at onset or whether there was a history of appendectomy [11]. These observations do not necessarily implicate causality.

The expected clinical behavior (B on the Montreal Classification) of UP can be inferred possibly from a recent report from the IBSEN group. In examining the course of UC in the large IBSEN UC cohort, it was shown that 55% of cases had a mild course after an initial severe episode, 37% had a chronic relapsing course, 6% had continuous disease activity, and 1% had a mild onset followed by a severe progression [7]. In the Copenhagen cohort 74% of patients has 2 or more relapses of UC per year [8]. It is likely that these data are applicable to cases of UP, but there is no study to date looking specifically at the behavior of UP over time.

Refractory UP is defined as more than three relapses per year, chronic disease activity on continuous medications, or need for systemic corticosteroid or immunomodulatory therapy [3]. It should be noted that the criteria for defining refractory UP are different from those pertaining to UC, since UP seldom presents with systemic features like fever or anemia. Of note, refractoriness was an independent predictor of proximal disease extension [11]. Refractoriness can be established after confounding issues like misdiagnosis and poor compliance are excluded, and there are objective signs of continuing illness like a raised ESR, CRP and calprotectin. Concomitant states like lactose intolerance and the irritable bowel syndrome must be excluded.

5. Principles of Treatment

The goals of treatment of UP are similar to those of treating ulcerative colitis, although it is stressed that patients with UP were in general excluded from trials of new therapies in patients with UC. The following are to be considered: clinical response, clinical remission, deep remission (mucosal healing), maintenance of remission, avoidance of surgery, quality of life, capacity to work, and psychological well-being. Lack of mucosal healing will invariably be followed by relapse. In all but the simplest cases a multi-disciplinary team may be required, including a nutritionist, social worker, psychologist, and occasionally a surgeon. It is important to select a definite time horizon per medication given and to review the patient's progress at fixed time intervals, while performing appropriate of tests and rectoscopy or sigmoidoscopy (sometimes also colo-

noscopy, always looking for proximal extension). It is necessary to monitor maintenance therapy like acute therapy, with frequent review of the patient's condition. Use of the Montreal and Mayo Classifications will assist in creating an objective record of the patient's condition.

Regueiro *et al.* [12] and Meier and Sturm [13] have published time-bound step-up algorithms for treating UP, which can be used to supplement the scanty ECCO guidelines on the subject. In the initial scenario, treatment with topical 5-ASA (5-aminosalicylic acid) is begun as suppository, enema or foam, in a dose range of 1 - 4 g/day. A good response is followed by maintenance 5-ASA in reduced dose, daily or every 2nd or 3rd day. In a second scenario, when the primary response to rectal 5-ASA is inadequate, oral 5-ASA is added, and if this does not induce a remission then rectal corticosteroids are used, such as hydrocortisone, prednisone, budesonide, betamethasone or beclomethasone, as suppository, enema or foam, often in combination with rectal or oral 5-ASA, to bring the disease into remission. In the third scenario, we are dealing with refractory proctitis; this demands the use of corticosteroids given orally. An inadequate result is followed by adding ciclosporin, tacrolimus or anti-TNFα and other biologic preparations (the order would depend on the experience of the treating physician). Then immunomodulators are added for long-term maintenance therapy. In the final scenario, proctocolectomy remains an option for severe cases. These steps will be discussed in more detail.

6. Topical Therapy

Trials of 5-ASA have usually involved the use of oral formulations, and describe all UC cases, not specifically UP. Ford *et al.* [14] have meta-analyzed the literature of the efficacy of oral 5-ASA, particularly mesalamine, in UC. In seven randomized controlled trials in UC, 5-ASA was significantly better than placebo in inducing remission; with 5-ASA the remission rate averaged 58% over 6 - 8 weeks of therapy. There was no statistical difference in efficacy between the various 5-ASA preparations used in these trials. Doses of ≥2.0 g/day were more effective than <2.0 g/day for bringing active disease into remission (RR = 0.91; 95% CI 0.85 - 0.98). Several oral 5-ASA preparations are available on the market. While their mode of delivery to the gut is different (pH-dependent, time-released, delivery by carriers) all are active in the colon. MMX mesalamine (LIALDA in the US; MEZAVANT in the EU) is a relatively new formulation. MMX mesalamine in a dose of 2.4 - 4.8 grams orally daily for 8 weeks was significantly better than placebo (40% versus 22%) in inducing clinical and endoscopic remission in a randomized trial of patients with active UC [15]. About 75% of these patients had distal colitis, but the proportion of UP was not defined.

However, this review is concerned with UP, and the rectal formulations of 5-ASA provide a higher concentration of active drug locally compared with oral formulations. Rectal 5-ASA is thus recommended as the first-line treatment for UP. Burger and Travis [16] recommend 5-ASA 1 gram suppository daily as the initial treatment for UP, with clinical remission being achieved in 64% of patients by 2 weeks. There is no dose

response to topical therapy above 1 g 5-ASA daily [13]. Nonetheless, higher doses can be tried when a lower does in not effective, since the amount of loss of drug into the stool is unknown. Suppositories act in the rectum, while foams and enemas spread in the entire sigmoid colon and the descending colon, respectively. When treatment with a suppository does not give the expected response in a compliant patient in 2 - 4 weeks, it is still worthwhile trying a foam or enema. Some patients have great difficulty using suppositories, and foam or enema may give better compliance.

Rectal 5-ASA is more efficacious for induction of remission in UP compared with oral 5-ASA, and compared with rectal corticosteroids [17]. The response to rectal 5-ASA 2 g per day was better than with hydrocortisone foam 100 mg: rectal bleeding and mucus abated more quickly with 5-ASA during the first 2 weeks of therapy, although there was no difference in histology between the treatment groups [18]. Rectal corticosteroids are indicated where rectal plus oral 5-ASA have failed, and it is possible to alternate rectal 5-ASA with rectal steroids. The combination of topical 5-ASA and topical corticosteroid leads to much greater rate of clinical and endoscopic improvement than use of either agent alone. The choice of rectal steroid is probably not important, and different countries have different formulations, but budesonide could also be considered (see below). A response should be achieved in up to one month.

7. The Refractory Patient

Refractory patients require systemic treatment with oral corticosteroids, even though the efficacy of such treatment in UP has not been examined specifically in any clinical trial. Dosage (recommended dose of 60 mg per day, tapering after a week) and duration of corticosteroid therapy are similar as in UC, and the intravenous route is an option in non-responsive patients. By adhering to defined dosage regimes within specified time frames, and using objective criteria for improvement or lack of response, it is possible to avoid steroid side-effects. Responding patients are weaned off corticosteroid while 5-ASA is continued or re-introduced. Failure of 5-ASA to maintain control of symptoms will mean that the patient must be offered an immunomodulator, 6-mercaptopurine or azathioprine. There are no specific trials of thiopurines in UP, but they are used as a steroid-sparing agent in maintenance treatment of UC and could be used as such in UP. Methotrexate has not been shown to have any benefit in UC [19].

Until recently, ciclosporin would next be offered to patients who do not respond to the treatments indicated. Nowadays, biologic therapy is the treatment of choice where corticosteroid therapy fails to control the disease. Ford *et al.* reviewed the remarkable efficacy of infliximab versus placebo in UC, but did not include any UP cases [20]. Bouguen *et al.* reviewed the use of infliximab in France. In a small series of 13 patients with steroid- and immunomodulatory-resistant UP, the response rate to infliximab was 11 out of 13, or 85% [21]. A case study showed that rectal infliximab can work where intravenous induction had failed. A 38-year old Hungarian female post-subtotal colectomy for UC received infliximab per rectum in the dose of 100 mg per day for 6 days, and improved both clinically and endoscopically [22]. A single-center study found no

difference in the efficacy of infliximab and adalimab in UC [23]. However, a recent meta-analysis in UC patients suggested that infliximab was statistically superior to adalimumab post-induction, golimumab was superior to adalimumab for sustained outcomes, and golimumab and infliximab were comparable in efficacy [24]. There is a need for specific studies of outcomes of UP patients treated with biologics, including the integrin inhibitor vedolizumab which is approved for use in anti-TNF resistant UC as well in anti-TNF naïve UC. As with all biologic therapies in inflammatory bowel disease, their high acquisition cost will likely limit their use in UP; most studies fail to show cost savings with these agents [25].

8. Novel Topical Therapies

There are a number of novel topical therapies for UP in the pipeline. Sandborn *et al.* recently reported the use of budesonide rectal foam in 72 mild-moderate UP and 193 distal colitis patients [26]. Budesonide foam is a new rectal preparation that delivers this drug up to a mean of 25 cm from the anal verge, providing uniform drug delivery (2 mg/25 ml) to the rectum and distal sigmoid colon. The drug was administered twice daily for 14 days, then once daily for 4 weeks. The primary endpoint of induction of remission was met in 41% of subjects taking the medication versus 24% in those receiving placebo; UP patients were not reported separately. Earlier reports had indicated that budesonide foam was as effective as enemas of hydrocortisone or budesonide for inducing remission in moderate UP. As the drug becomes more widely available it will be interesting to follow its efficacy in multiple cases of UP that fail to respond to 5-ASA given rectally.

Other new topical agents have been proposed for the management of resistant UP, including enemas with butyrate, ciclosporine, nicotine, lidocaine and bismuth, but there is no controlled study of any of these. Ciclosporine has of course been used systemically, but its use is complicated and requires careful selection of patients and strict monitoring in hospital, and it will likely be replaced entirely by the biologics. Tacrolimus was successfully used intra-rectally in an eight-year old girl with refractory UP; the dose of 2 mg was administered nightly over 4 weeks [27]. Rifaximin was statistically better than placebo in acute UC [28]. However, UP was not specifically studied.

There is some evidence that elective appendectomy may benefit refractory UP. In a novel approach, 30 adults on medical treatments for UP underwent removal of the appendix, with improvement of their symptoms, such that most were able to stop all their medications [29]. In a further report, 8 patients with refractory UP underwent elective appendectomy; healing of the proctitis ensued and was maintained with a follow-up period of over 3 years [30]. The mechanism in these cases in not quite understood, but in both cases series there was definite evidence of inflammation in the appendix (but not acute appendicitis), suggesting a possible bacterial link. As is well known, appendectomy at an early age is protective against UC [31]. This approach requires further validation in refractory UP patients.

Enteral nutrition was reported to be of benefit in some cases of UP, but parenteral

nutrition is not advised. This requires further study. The association of smoking with reduction of symptoms and inflammation in UC was noted above, but there have not been any studies to date of the potential benefit of smoking in severe UP patients.

Peyrin-Biroulet *et al*. have just published a very comprehensive consensus guideline for the treatment of UC and UP [32]. Based on the majority opinions of 37 leading experts in the field, an algorithm was designed highlighting the management of refractory UP. Refractory UP was defined as a lack of response to two months of topical 5-ASA ± oral 5-ASA, and one month of topical corticosteroids. The next advised treatment step was azathioprine, and then the addition of anti-TNF*α*. Opimization of anti-TNF*α* was advised, according to current practice, as was switching between anti-TNF*α* agents as required, and the introduction of vedolizumab for anti-TNF*α* non-responders. Fewer than half the panel of experts advocated methotrexate or surgery for ultimate non-responders. This algorithm is reasonable and reflects current practice. However, as intimated above, there are some new avenues of treatments not considered in the algorithm. Furthermore, newer biologics will become available in the near future, and if appendectomy proves to be successful in larger patients cohorts then it will certainly be a better alternative than colectomy.

While 5-ASA is usually an innocuous medication, this is not true of most of the other therapies considered herein [33]. Indeed, several therapies have the potential for serious side-effects, some of which could be life-threatening. Principally, the immunomodulators and biologics require special consideration. Proper screening of patients for tuberculosis, hepatitis and other infections, and malignancies including non-melanotic skin cancer is a prerequisite before beginning treatment. Patients should be seen by a dermatologist periodically. Patients are to be warned about possible infections developing while on treatment. Prolonged use of corticosteroids can lead to side-effects as well, including budesonide. Calcium and vitamin D are administered as required.

9. Conclusion

The approach to treating UP is not simple. Given that not a few patients are resistant to rectal 5-ASA, there will be a need for local steroid treatment and for systemic steroids, and for biologics in some cases. Accurate diagnosis and re-diagnosis is necessary, with the use of endoscopy to monitor mucosal healing, and with an eye on the differential diagnosis at all times. Patients with UP often become despondent when there is no rapid resolution of symptoms, and this can severely affect their relationships with family and friends, and impair their ability to work. UP remains a challenge for the gastroenterologist. It is anticipated that more effective treatment will be developed in the near future.

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List of Abbreviations

UC, ulcerative colitis,

UP, ulcerative proctitis,

Montreal classification (E, S, A), extent, disease activity, patient age,

ECCO, European Crohn's Colitis Organization,

5-ASA, 5-aminosalicylic acid,

RR, relative risk,

CI, 95% confidence intervals,

anti-TNFα, anti-tumour necrosis factor alpha.